D-based KIE in Total Synthesis

Outline:

1. Introduction to KIE

Primary and Secondary KIE

2. Use in Total Synthesis:

1991, Clive: fridericamycin A

2002, Danishefsky: guanacastepene A

2002, Vedejes: aziridinomitosenes

2004, Miyashita: norzoanthamine

2012, Garg: welwitindolinones

2016, Micalizio: *Seco*-prezizaane Sesquiterpenes

2016, Burns: danicallpin A

2020, Baran: taxol

Not covered:

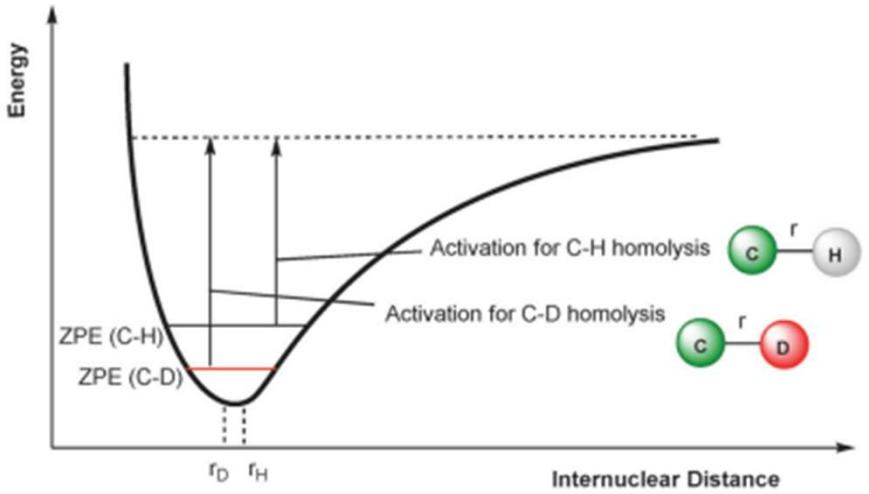
2022, Luo: mutilin

Useful Reviews:

Atzrodt, J., *et al. Angew. Chem. Int. Ed.,* **2018**, *57,* 1758. https://doi.org/10.1002/anie.201704146.

Wiberg, K. B. *Chem. Rev.,* **1955**, *55,* 713. https://doi.org/10.1021/cr50004a004

Introduction:



- Kinetic isotope effect (KIE) is observed in between the isoptopically labelled molecules showing different reaction rates.
- Primary KIE is attributed to a bond breaking event at the C-H/C-D bond.
- Vibrational frequency is relative to reduced mass μ
  - For C-D, lower vibrational frequency and lower zero-point energy (ZPE)

$$\mu = \frac{m1 \bullet m2}{m1 + m2} \qquad E_n = (n + 1)h\nu$$

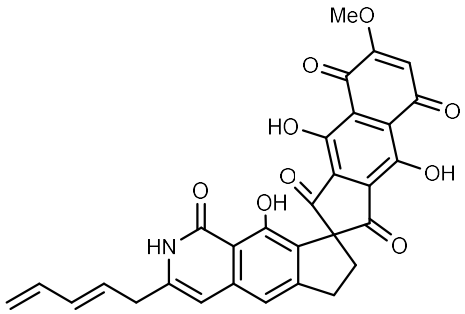
$$\mu_{C\text{-}H} = 0.92 \qquad \nu = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$$

$$\mu_{C\text{-}D} = 1.71$$

- Secondary KIE arises when the C-H/C-D bond remains intact during the rate limiting step
  - Produced upon changes in hybridization or through involvement of hyperconjugation

D-based KIE in Total Synthesis

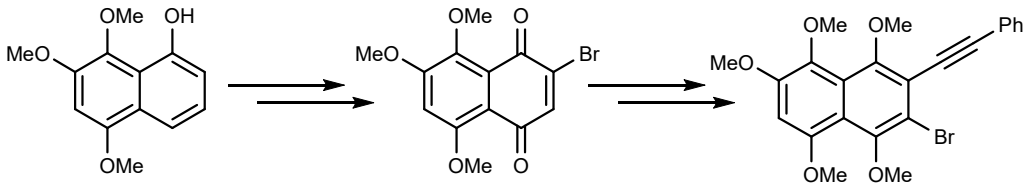
Fridericamycin A



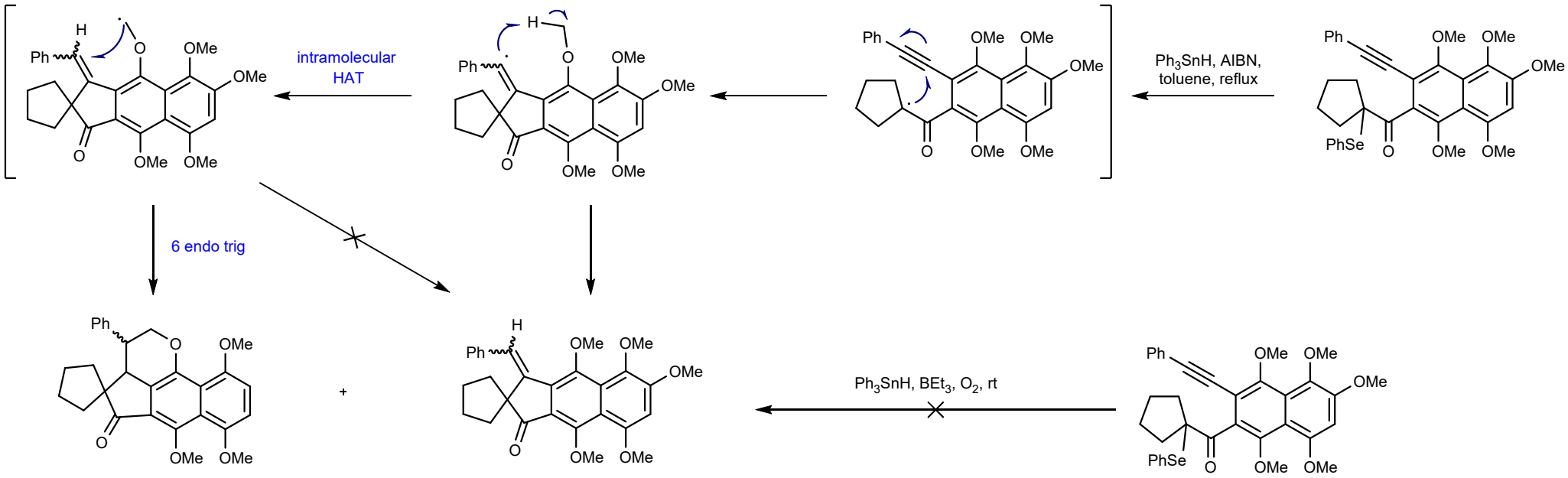
Fredericamycin A

- Fungal metabolite isolated from a strain of *Streptomyces griseus* (from a soil sample in Frederick, MD)
- Possesses antibiotic properties
- Powerful antitumor agent

1991, Clive:



"Preparation of the bromide… proved extremely troublesome task. It was the most time-consuming part of the synthesis, and it required a resolute effort to find a convenient route."

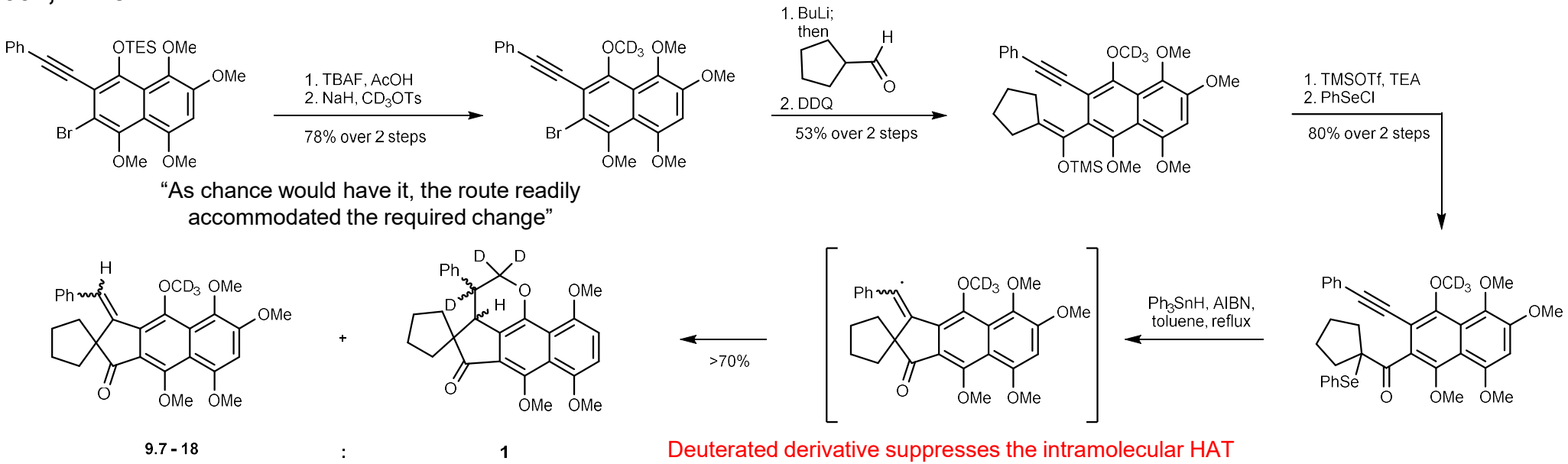


Radical generation under milder conditions was not possible
Attempts to protect phenols as acetals were unsuccessful

Clive, D. L. J. *J. Chem. Soc., Perkin Trans. 1,* **1991**, 1433. https://doi.org/10.1039/P19910001433. Clive, D. L. J. *J. Chem. Soc., Chem. Commun.,* **1991**, 1755. https://doi.org/10.1039/C39910001755. Clive, D. L. J. *Tetrahedron* **1993**, *49*, 7917. https://doi.org/10.1016/S0040-4020(01)88016-9.

D-based KIE in Total Synthesis

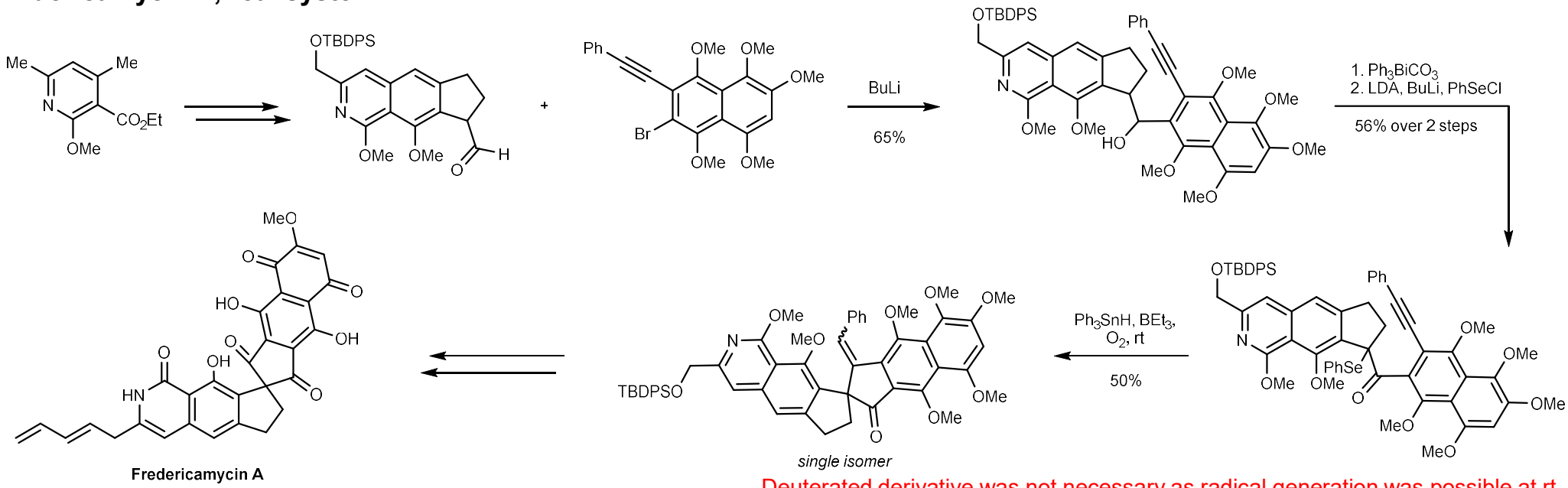
1991, Clive:



"As chance would have it, the route readily accommodated the required change"

Deuterated derivative suppresses the intramolecular HAT

Fridericamycin A, real system:

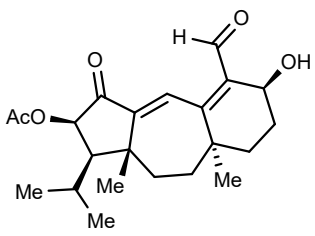


Deuterated derivative was not necessary as radical generation was possible at rt

Clive, D. L. J. *J. Am. Chem. Soc.* **1994**, *116*, 11275. https://doi.org/10.1021/ja00104a009

D-based KIE in Total Synthesis

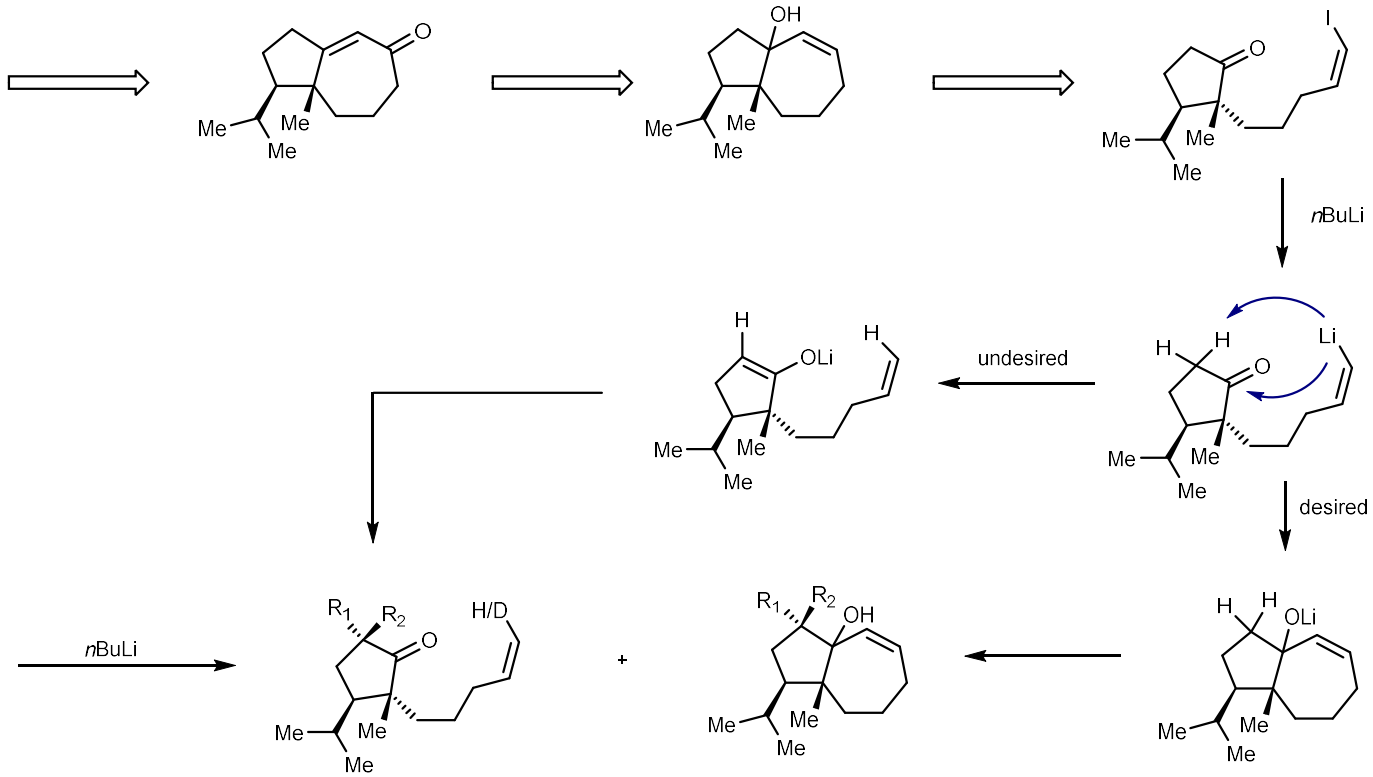
Guanacastepene A



guanacastepene A

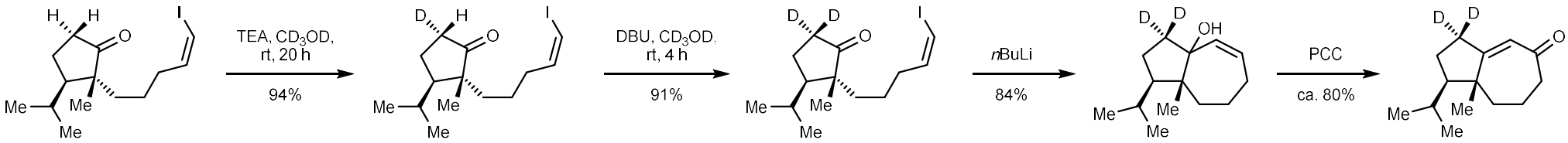
- Diterpene natural product produced by endophytic fungus in Costa Rica
- Showed activity against antibiotic-resistant bacteria and hemolytic activity against red blood cells
  - Likely due to nonspecific membrane lysis

2002, Danishefsky:



R_1, R_2 =	Yield	Ratio	Yield
$R_1 = R_2 = H$	18%	22 : 78	65%
$R_1 = D$, $R_2 = H$	9.3%	12 : 88	71%
$R_1 = R_2 = D$	8.6%	9 : 91	84%

Deuterated derivative suppresses the undesired lithiation

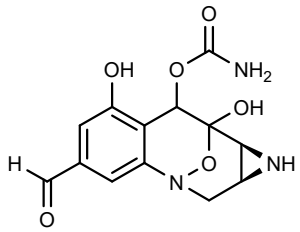


Danishefsky, S. J. *Tett. Lett.* **2002**, *43*, 5605. https://doi.org/10.1016/S0040-4039(02)01114-0

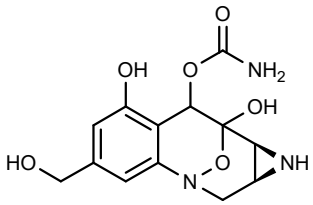
D-based KIE in Total Synthesis

Aziridnomitosenes

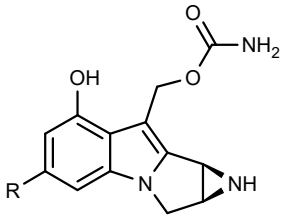
Potent antitumor activity:



FR900482

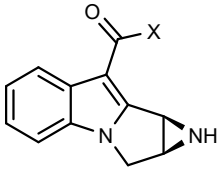


FR66979

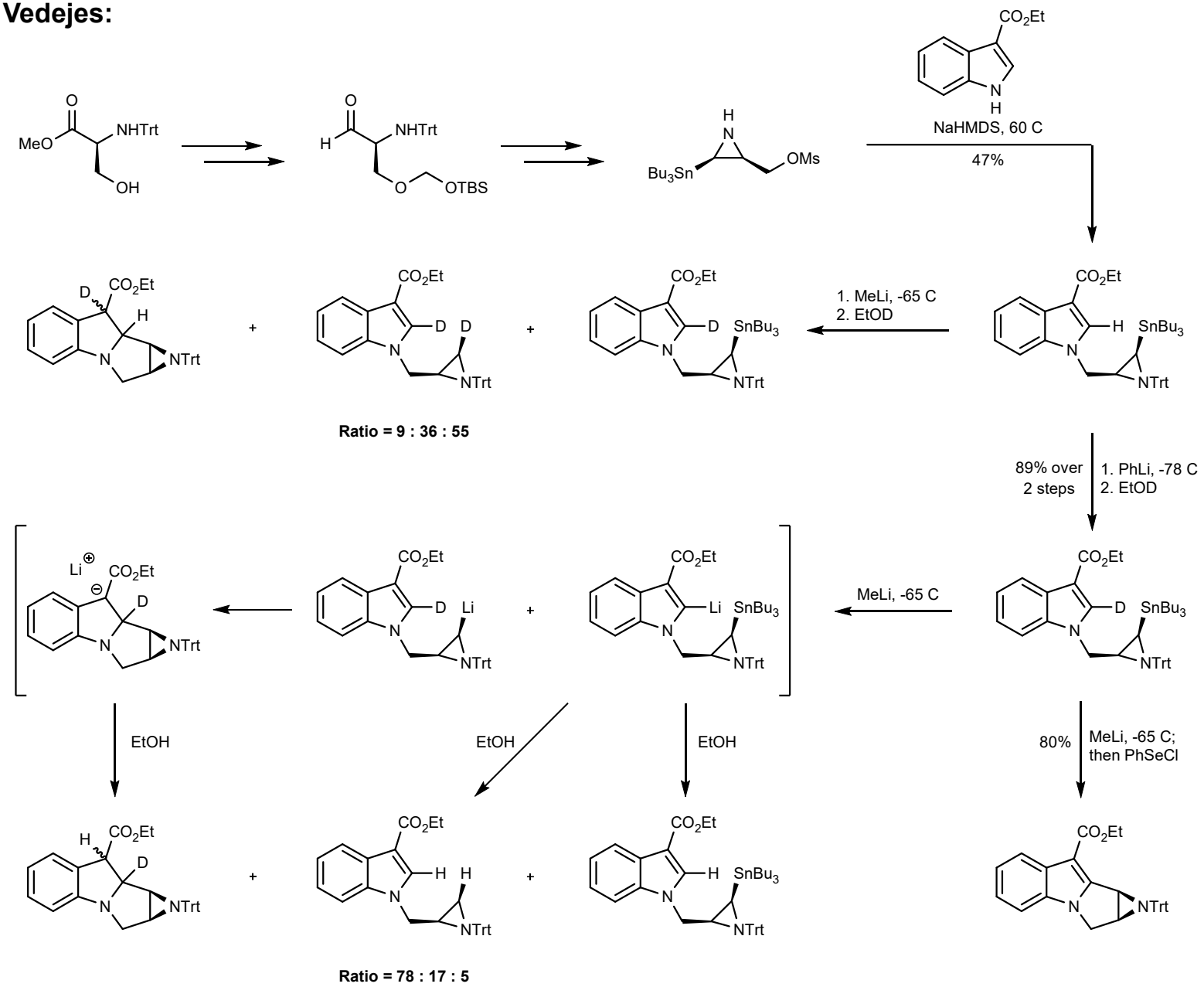


Hypothesized intermediate that can cross-link DNA

Target structure:



2002, Vedejes:

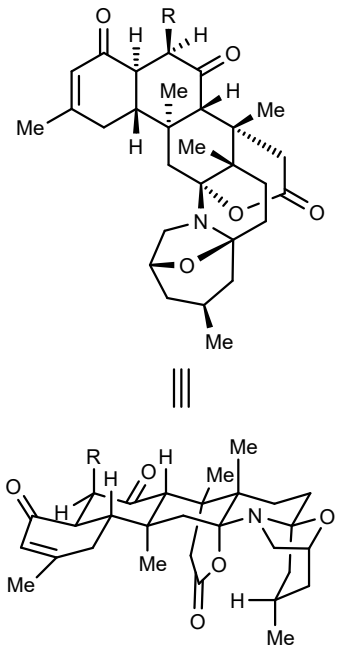


Deuterated derivative suppresses the undesired lithiation

Vedejes, E. *J. Am. Chem. Soc.* **2002**, *124*, 748. https://doi.org/10.1021/ja0120835. Vedejes, E. *J. Org. Chem.* **2004**, *69*, 1788. https://doi.org/10.1021/jo030224a
Vedejes, E. *J. Org. Chem.* **2004**, *69*, 1794. https://doi.org/10.1021/jo030223i

D-based KIE in Total Synthesis

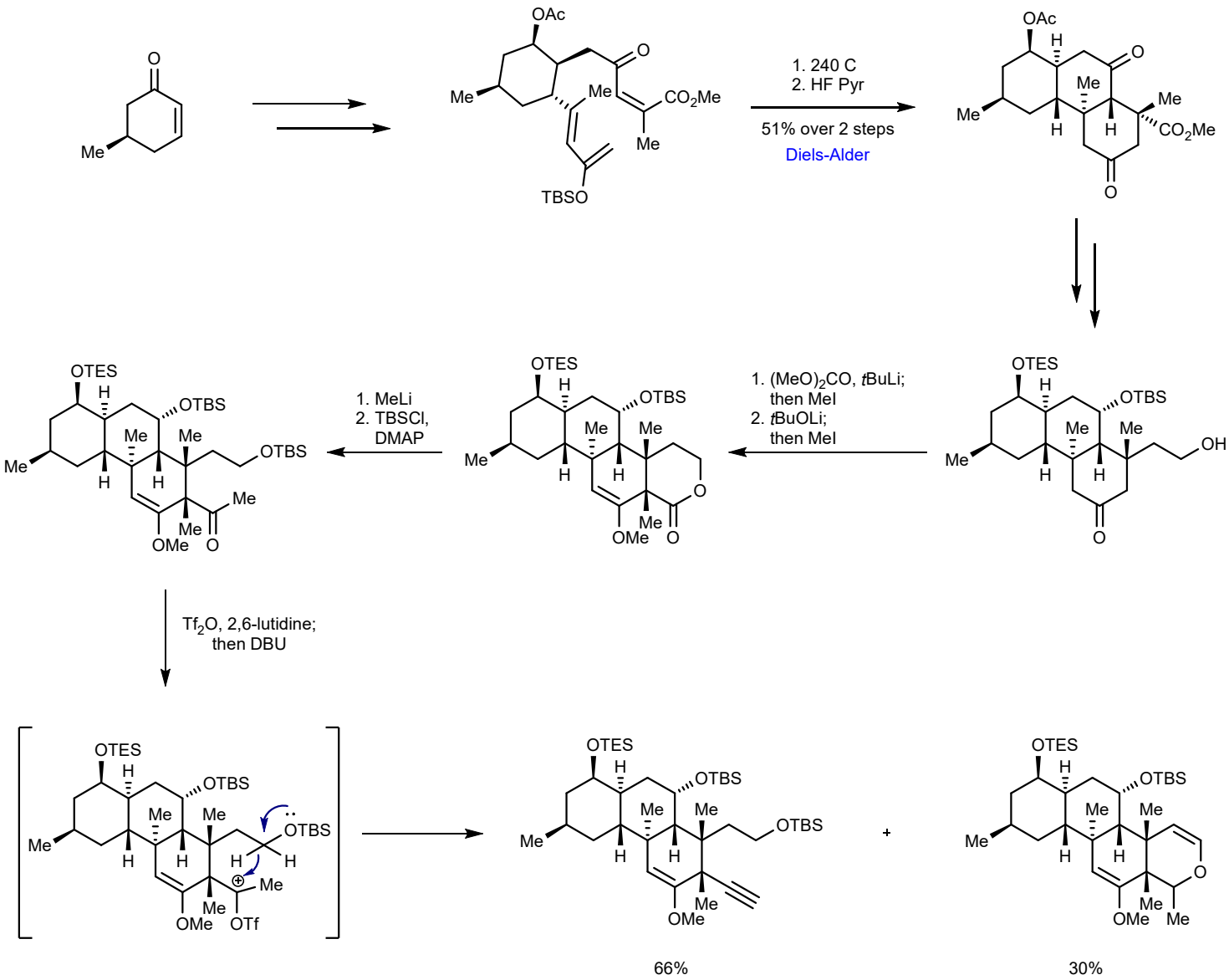
Norzoanthamine:



R = H = Norzoanthamine
R = Me = Zoanthamine

- Heptacyclic marine alkaloids isolated from *Zoanthus* species
- Norzoanthamine can suppress the loss of bone weight and strength in ovariectomized mice
- Zoanthamine has exhibited powerful analgesic effects as well as potent inhibitory activity toward phorbol myristate-induced inflammation
- First total synthesis: 41 steps with 3.5% overall yield (2002, Miyashita)

2004, Miyashita:

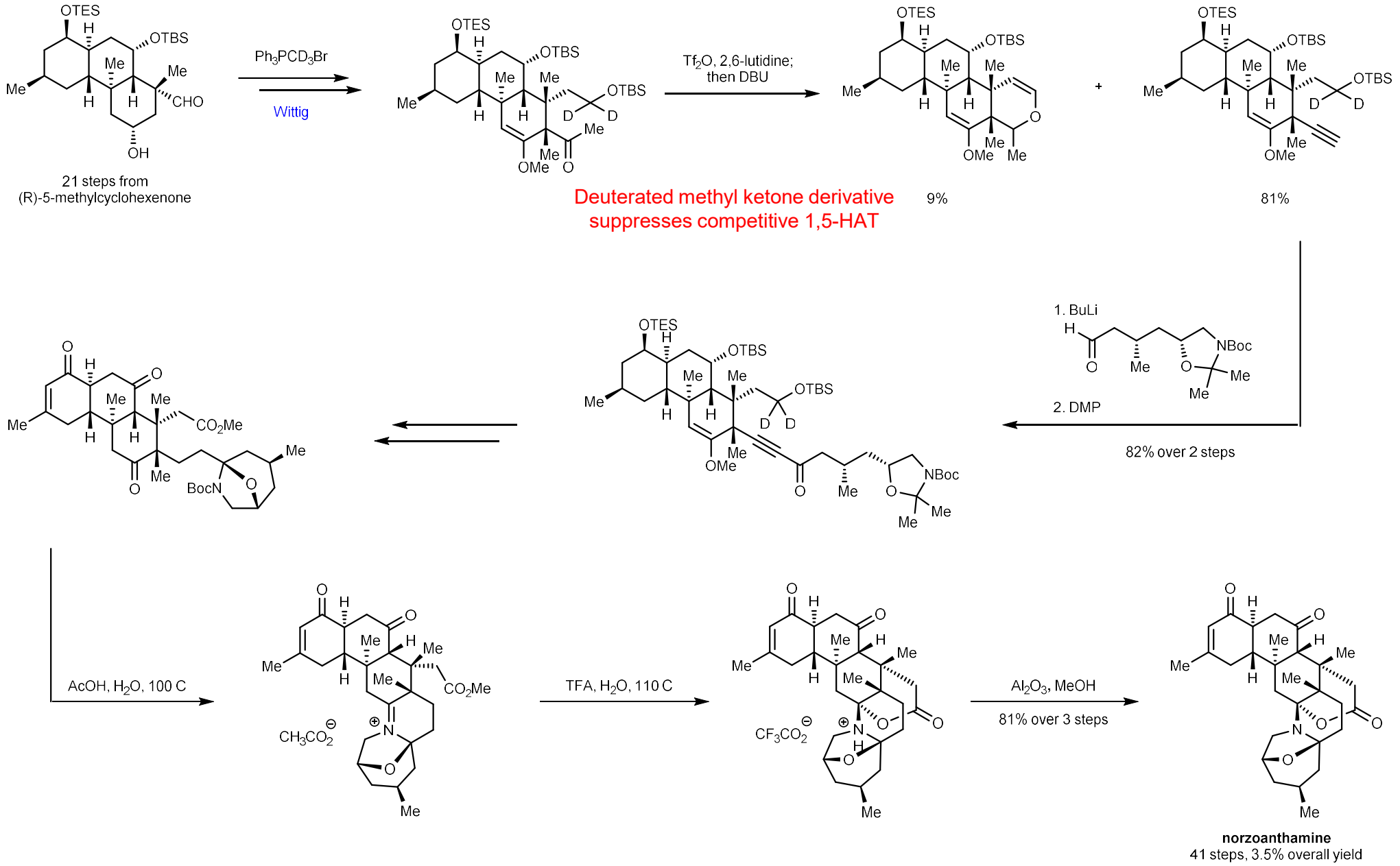


Nondeuterated methyl ketone derivative displayed competitive 1,5-HAT

Miyashita, M. *Science* **2004**, *305*, 495. https://www.science.org/doi/10.1126/science.1098851

D-based KIE in Total Synthesis

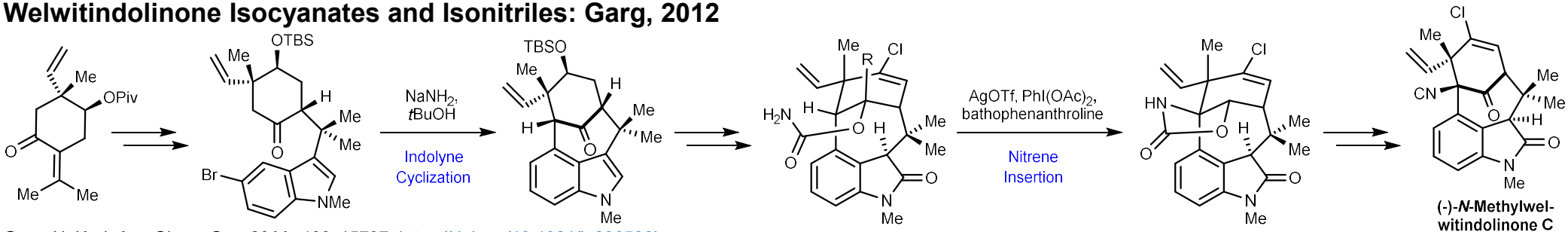
Norzoanthamine: 2004, Miyashita



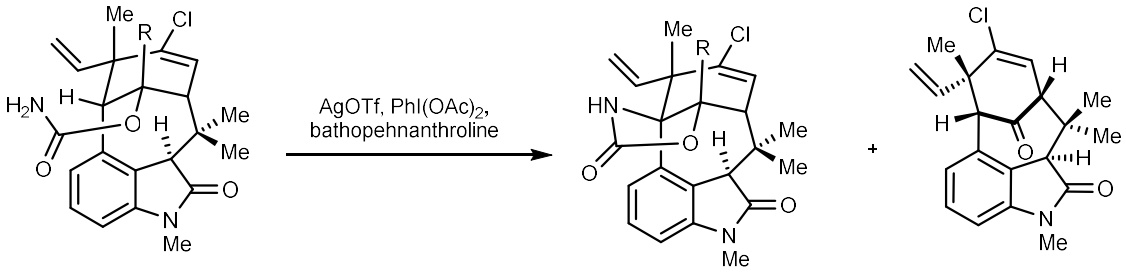
Miyashita, M. *Science* **2004**, *305*, 495. https://www.science.org/doi/10.1126/science.1098851

D-based KIE in Total Synthesis

Welwitindolinone Isocyanates and Isonitriles: Garg, 2012

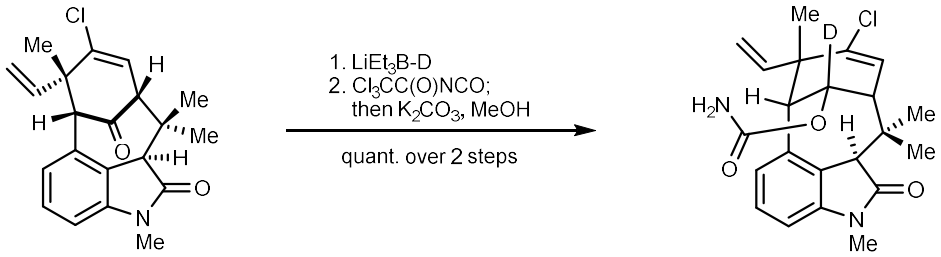


Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797. https://doi.org/10.1021/ja206538k



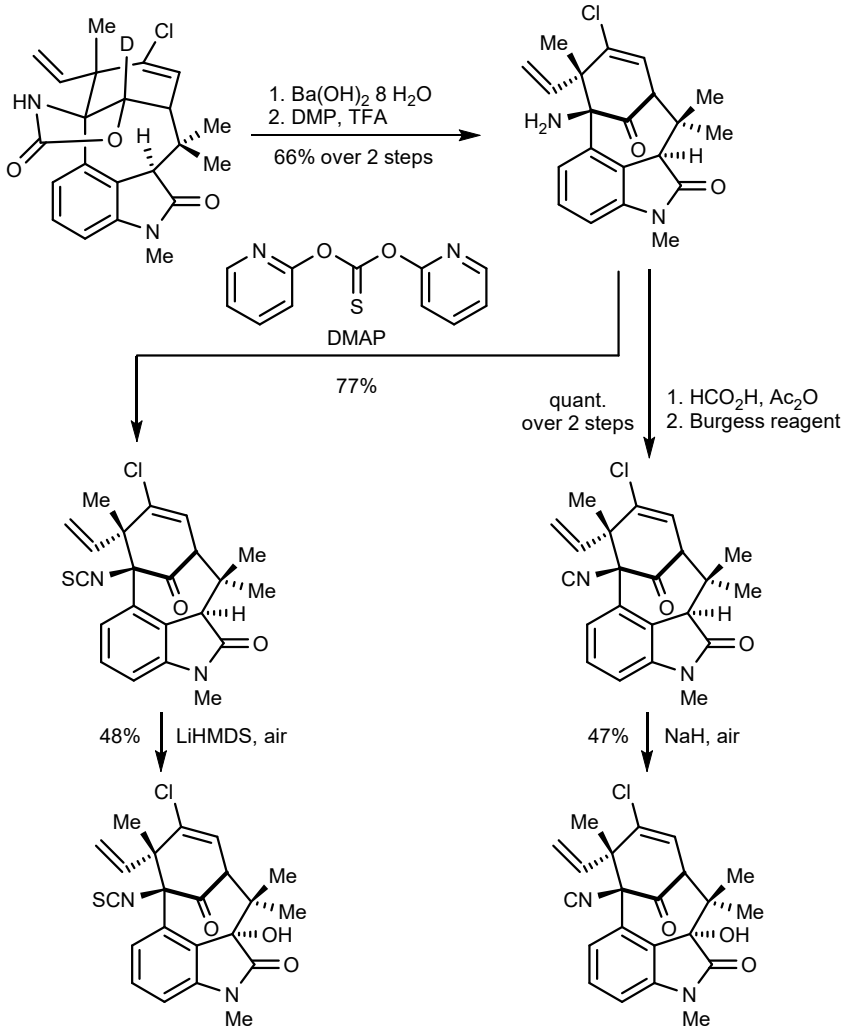
R =	Yield	Ratio	Yield
R = H	33%	1.3 :1	25%
R = D	60%	7.5 : 1	8%

Deuterated derivative suppresses the undesired insertion of intermediate nitrene species into the C10 C-H bond



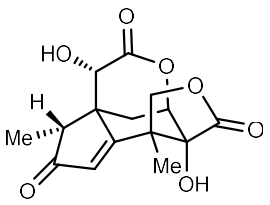
"The strategic use of a deuterium kinetic isotope effect in total synthesis is rare, and the present study marks the first use of this approach to facilitate a C−H functionalization event en route to natural products"

Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396. https://doi.org/10.1021/ja210837b

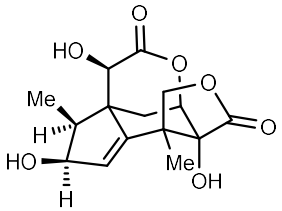


D-based KIE in Total Synthesis

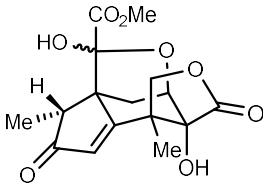
Seco-prezizaane Sesquiterpenes



(*1R, 10S*)-2-oxo-3,4-dehydroneomajucin



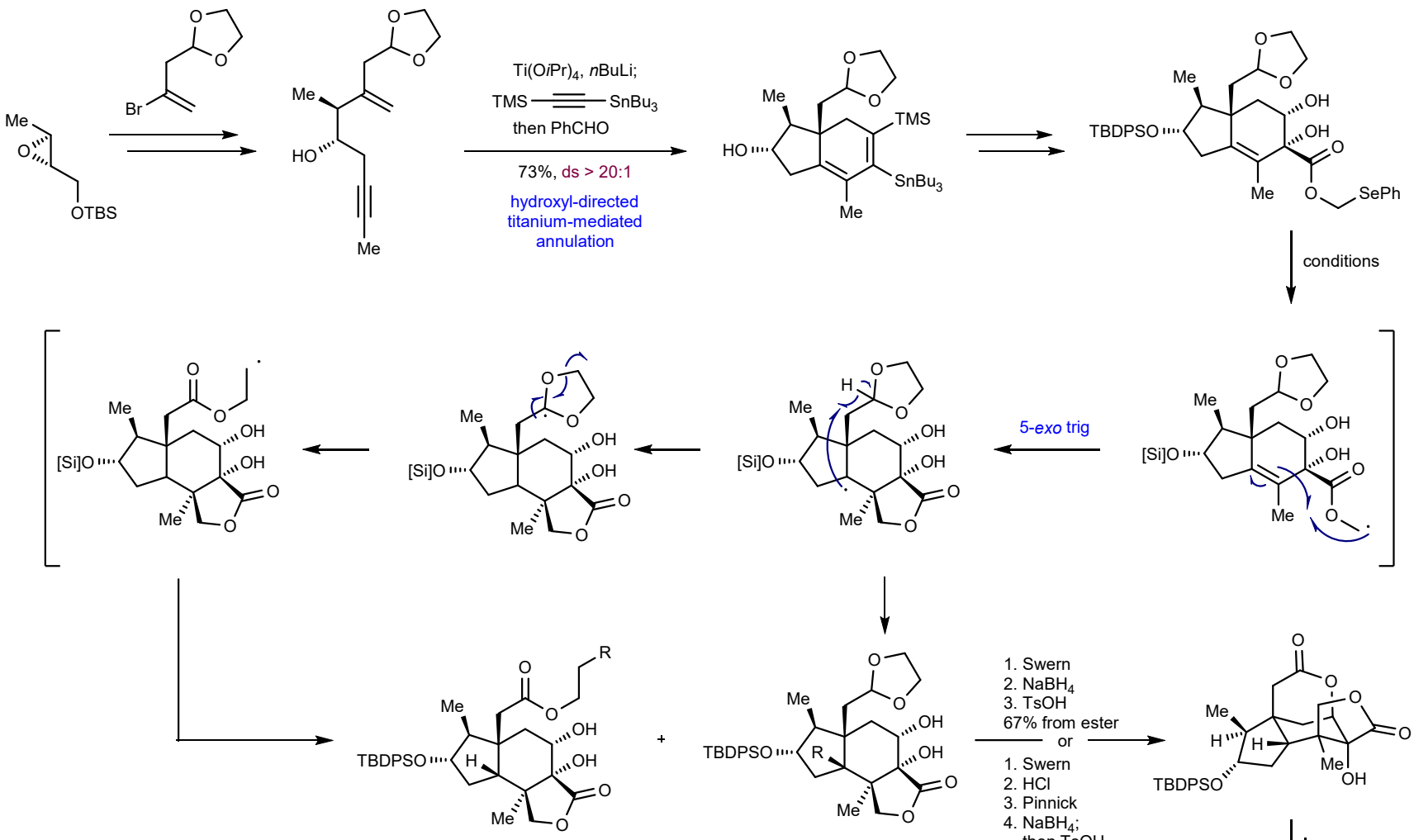
(*2S*)-2-hydroxy-3,4-dehydroneomajucin



(-)-jiadifenin

- Isolated from the dried fruit of the Chinese *Illicium majus*
- Possesses potent neurotrophic properties
- Doesn't exhibit convulsive toxicity in mice

2016, Micalizio:



Conditions	R =	Ratio
AIBN, Bu_3SnH	R = H	1 : 1
AIBN, Bu_3SnD	R = D	1.4 : 1
AIBN, TMS_3SiH	R = H	4.7 : 1

(*1R, 10S*)-2-oxo-3,4-dehydroneomajucin

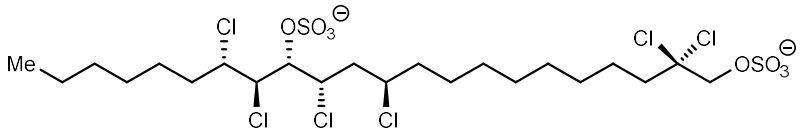
(*2S*)-2-hydroxy-3,4-dehydroneomajucin

(-)-jiadifenin

Micalizio, G. C. *J. Am. Chem. Soc.* **2016**, *138*, 1150. https://doi.org/10.1021/jacs.5b12694

D-based KIE in Total Synthesis

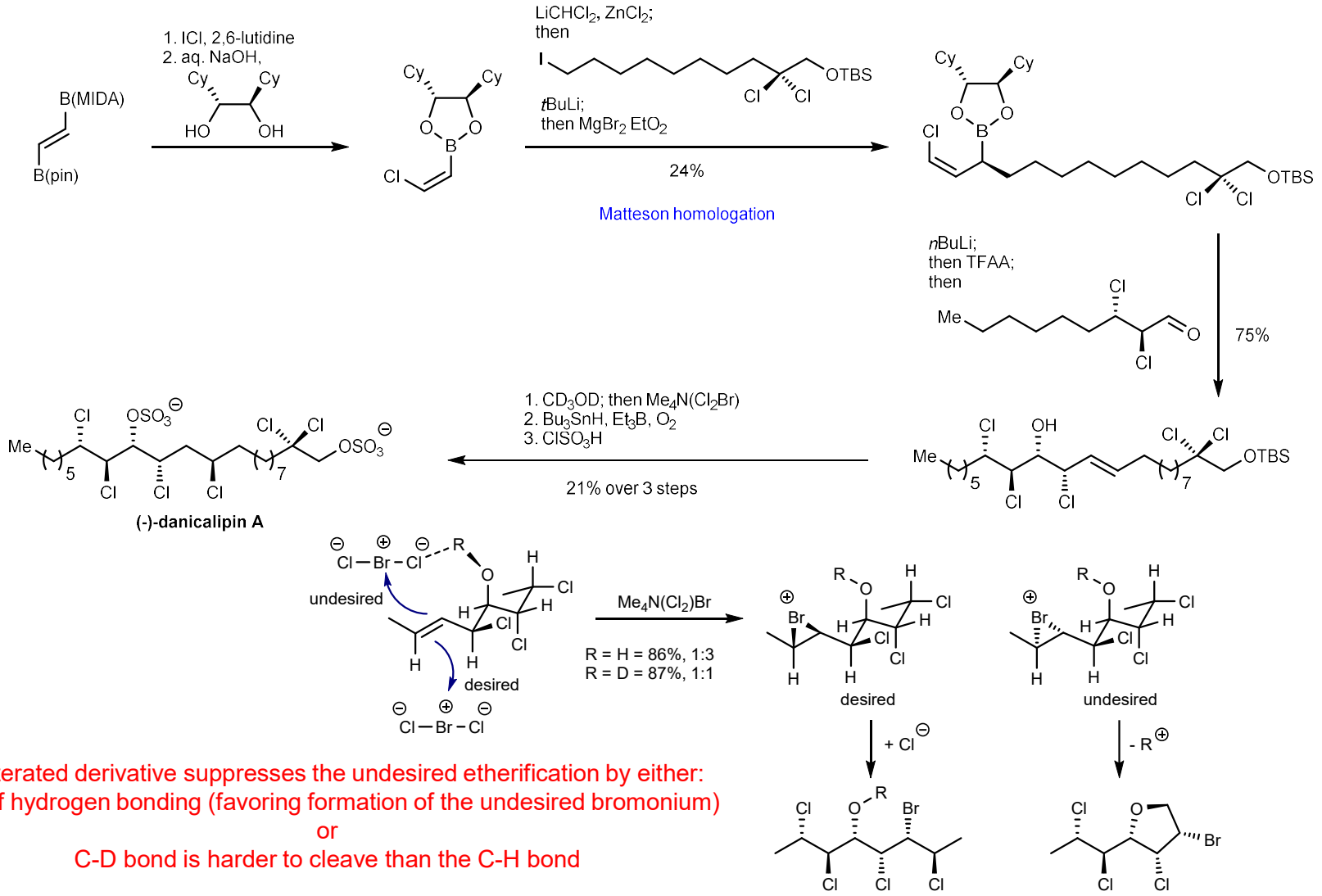
(−)-Danicalipin A:



(-)-danicalipin A

- Chlorosulfolipid
- Estimated to comprise >90% of all polar lipids in the flagellar membrane of *Ochromonas danica* (freshwater algae)
- 5 reported syntheses, prior to this report
  - Most efficient: 9 (Vanderwal) and 12 (Carreira) steps

2016, Burns:

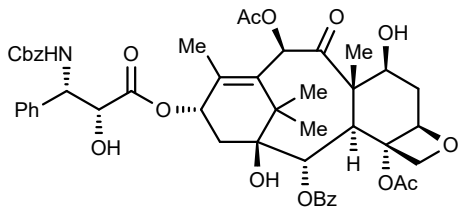


Deuterated derivative suppresses the undesired etherification by either:
lack of hydrogen bonding (favoring formation of the undesired bromonium)
or
C-D bond is harder to cleave than the C-H bond

Burns, N. Z. *J. Am. Chem. Soc.* **2016**, *138*, 5150. https://doi.org/10.1021/jacs.6b01643

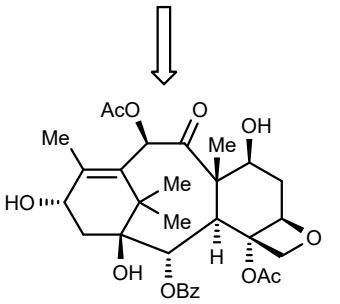
D-based KIE in Total Synthesis

Taxol, Baran 2020:

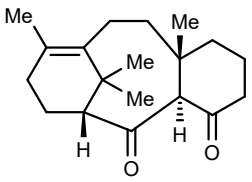


Taxol

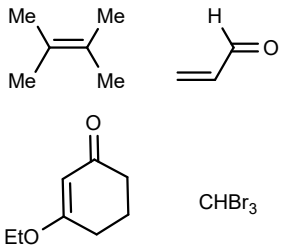
"the C2 α-deuterium atom, which served as the smallest 'protecting group' that kinetically guided the C1 oxidation"

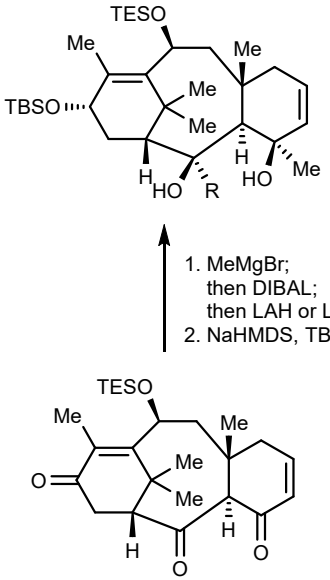


oxidase phase



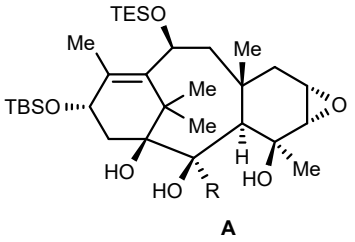
cyclase phase



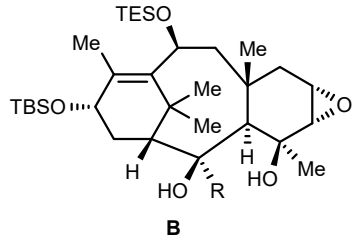


1. MeMgBr; then DIBAL; then LAH or LAD
2. NaHMDS, TBSCl

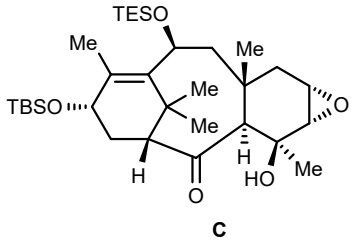
conditions



A



B



C

Deuterated derivative suppresses the undesired oxidation

R =	Conditions	Results (% yield A/B/C)
R = H	DMDO in acetone (0.09 M)	25% / 45% / 10%
R = D	DMDO in acetone (0.09 M)	9% / 12% / 37%
R = D	DMDO in DCM (0.21M)	29% / 11% / 12%
R = D	DMDO in $CHCl_3$ (0.19 M)	34% / 15% / 10%
R = D	DMDO in $CHCl_3$ (0.30 M)	49% / 8% / 11%

Baran, P. *J. Am. Chem. Soc.* **2020**, *142*, 10526. https://doi.org/10.1021/jacs.0c03592. Baran, P. *J. Org. Chem.* **2020**, *85*, 10293. https://doi.org/10.1021/acs.joc.0c01287